REMARKS

Claim Amendments

Claim 22 has been amended to correct obvious typographical and grammatical errors.

Claim 25 has been amended by deleting the phrase "derived from".

Claim 27 has been amended to have correct dependency.

Claim Rejections Under 35 U.S.C. §103(a)

Rejections of Claims 22, 24-26, 28-31, 32, 34, 36, 37 and 39-41 under 35 U.S.C. §103(a)

Claims 22, 24-26, 28-31, 32, 34, 36, 37 and 39-41 are rejected under 35 U.S.C. §103(a) as being unpatentable over Brambilla *et al.* (WO 00/41477, "Brambilla") in view of Brake *et al.* (Proc. Natl. Acad. Sci. USA, 81, 4642-4646, 1984, "Brake") or Stark *et al.* (EMBO J., 5, 195-2002, 1986, "Stark").

The Examiner stated that this rejection is maintained essentially for the reasons made of record in the previous Office Action, mailed December 13, 2007, with "slight" modifications, due to Applicant's amendments to the claims.

The Examiner stated that Brambilla discloses methods of production of a protein comprising the steps of culturing a *Z. bailii* strain, expressing a protein, and isolating a protein. The Examiner indicated that the difference between Brambilla and the instant claims is that Brambilla does not disclose that a protein is secreted and that a signal sequence such as the signal sequence shown in SEQ ID NO:1, or the pre-pro alpha-factor of S. cerevisiae, or the pre-sequence of the alpha-subunit of the K1 killer toxin of D. lactis, is operably linked to the DNA encoding the protein. The Examiner stated that Brake discloses the use of the signal and pre-pro sequence of the gene encoding alpha-factor mating pheromone to direct secretion of heterologous genes in yeasts. The Examiner stated that Stark discloses the signal sequence of the alpha-subunit of the K1 killer toxin of *K. Lactis* and its function in secretion of proteins. The Examiner stated that it would have been obvious for one of ordinary skill to have placed the signal sequence of Stark in operable linkage to a protein and a promoter of interest. The Examiner stated that it would have been obvious for one of ordinary skill to employ a well

known signal sequence disclosed by Brake within the system of Brambilla to direct the secretion of proteins of interest.

Applicants respectfully disagree with the Examiner's allegation for the following reasons.

Under recent United States case law, specifically, *KSR International Co. v. Teleflex Inc.*, 550 U.S.__, 82 USPQ2d 1385 (2007), regardless of the particular rationale used, a finding of unpatentability requires an Examiner to show, among other findings, a finding that one of ordinary skill in the art could have pursued known options or combined known elements *with a reasonable expectation of success.* At minimum, the person of ordinary skill in the art, in attempting to apply the teachings of Brake and Stark to the *Z Bailii* expression system taught by Brambilla, would have had an *unreasonable* expectation of success.

Brake teaches that use of the signal sequence of pre-pro α-factor of S. *cerevisiae* promotes the secretion of human epidermal growth factor from *S. cerevisiae*, *not* from other yeast species, let along other yeast genera. Similarly, Stark teaches that use of the signaling pre-sequence of the α-subunit of K1 killer toxin from *K. lactis* promotes the secretion of the α-subunit of K1 killer toxin from *K. lactis, not* from other yeast species, let alone other yeast genera.

The person of ordinary skill in the art is aware that yeast of different species and especially different genera are expected to have structural and functional differences between homologous or analogous proteins. Furthermore, Brake teaches that "the yeast secretory pathway involves a series of membrane-bound structures... [and] a membrane-bound protease" (page 4642, first column, first paragraph), thereby implying that any yeast is expected to have at least three proteins in its secretory pathway (at least two in the series and the membrane-bound protease).

In light of the teachings of the references and the knowledge of the person of ordinary skill in the art, such a person having only Brambilla, Brake, and Stark before him could *not* have had a reasonable expectation that secretion of proteins *Z. Bailii* could be effected by use of a signal sequence from either *S. cerevisiae or K. lactis.* A signal sequence from either *S. cerevisiae or K. lactis* would have to interact with at least three proteins in the *Z. bailii* secretory pathway that were sufficiently identical to analogous proteins from the *S. cerevisiae or K. lactis* secretory pathways to yield a comparable function. Brambilla, Brake, and Stark together *fail* to

provide the person of ordinary skill in the art with any reasonable expectation that such a comparable function would be yielded. Therefore, they fail to render the present claims unpatentable under any standard requiring a finding of a reasonable expectation of success set forth by the court in *KSR*. Therefore, Claims 22, 24-26, 28-31, 32, 34, 36, and 39-41 are patentable over the references of record. Reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

Rejection of Claim 27 under 35 U.S.C. §103(a)

Claim 27 is rejected under 35 U.S.C. §103(a) as being unpatentable over Brambilla, in view of Brake, or Stark, and in further view of Jacobson *et al.* (WO 92/04461, "Jacobson").

The Examiner stated that Brambilla, Brake and Stark are cited essentially for the reasons set above. The Examiner relies on the teachings in Jacobson of a DNA sequence comprising at least 35 nucleotides of the SEQ ID NO: 69, which is claimed in Claim 27.

Regarding the rejection of Claim 27, Applicants maintain their view that it is non-obvious for the same reasons as its base Claim 22, as discussed above. The person of ordinary skill in the art would recognize the DNA sequence of Jacobson as one that may be useful to express and secrete a protein of interest, but would further recognize that Jacobson fails to give the person of ordinary skill in the art any information regarding secretion of proteins from yeast.

Applicants submit that Claim 27, which depends on base Claim 22 is non-obvious over the cited references for the same reasons as base Claim 22. Reconsideration and withdrawal of the rejections are respectfully requested.

Claim Rejections Under 35 U.S.C. §112

Rejection of Claims 22, 24-30, 32, 34, 36, and 38-41 under 35 U.S.C. §112

Claims 22, 24-30, 32, 34, 36, and 38-41 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement.

The Examiner stated that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed.

The Examiner has recognized that the person of ordinary skill in the art has "high skill"(see page 6, line 15 of the Office Action mailed on July, 24 2008). By "high skill' Applicants presume that the Examiner means a person having at least about four years of post-graduate experience in the biotechnological arts relating to yeast and the expression of proteins herein, such experience comprising at least a master's degree and relevant work experience. Further, the Examiner is reminded that: "A person of ordinary skill is also a person of ordinary creativity, not an automaton." *KSR, supra.* In addition, the Examiner is reminded that information well-known in the art need not be repeated in detail in the written description of the invention.

The Examiner alleged that the specification fails to provide sufficient description of a sufficient number of species of vector usable in the claimed process to encompass the genus of vectors received by the claims.

Applicants respectfully disagree with this Examiner's position. As discussed above, the person or ordinary skill in the art has high skill and ordinary creativity and would understand the inventors had possession of the claimed invention, including any of the genus of vectors as discussed in the specification: page 5, line 31 through page 9, line 2.

Specifically, the specification teaches a method for producing a protein using the yeast *Zygosaccharomyces bailii*. In the method, a *Z. bailii* strain transformed with a vector comprising a DNA sequence coding for a protein functionally linked to a signaling sequence selected from the group consisting of the signaling presequence of the α-subunit of the K1 killer toxin of *Kluyveromyces lactis* and the signal sequence of the pre-pro α-factor of *Saccharomyces cerevisiae,* and further functionally linked to a promoter, is cultured. The protein is expressed and secreted by the transformed *Z. bailii.* Also, the protein is isolated.

The specification also teaches a method comprising culturing *a Zygosaccharomyces bailii* strain, expressing and secreting a protein, and isolating the protein, wherein the *Z. bailii* strain has been subjected to a selection process for improved secretion.

The specification also teaches the *Z. bailii* strain referred to above.

The specification exemplifies the use of *Z. bailii* vector pZ_3, for example, in Example 1, pages. 21-26 of the specification. The specification also exemplifies the production of Z. bailii vectors pEZ_1 and pEZ_2, for example in Example 9, pages 35-38 of the specification.

Furthermore, the specification reveals that *Z. bailii* gene expression and secretion of expressed protein are essential to the function/operation of the claimed invention. A particular nucleic acid is not essential to the claimed invention.

For reasons set forth above, the claimed method of protein production in *Z. bailii* is fully described. Independent Claim 22 is drawn to a genus, *i.e.*, any of a variety of methods that can be used for producing protein in *Z. bailii.* Three embodiments are actually reduced to practice. Namely, interleukin 1-β, glucoamylase and β-galactosidase are produced by *Z. bailii* (see Examples 3-6, pages 27-33).

The art indicates that there is no substantial variation within the genus because there are a limited number of ways to practice the process steps of the claimed invention.

The three embodiments are representative of the genus based on the disclosure of *Z. bailii* as a gene expression and secretion system, considered along with the level of skill and knowledge in the gene expression art discussed above. One of skill in the art would recognize that Applicants were in possession of all of the various expression methods necessary to practice the claimed invention.

In the view of above, Claims 22, 24-30, 32, 34, 36, and 38-41 are in compliance with the written description requirement. Reconsideration and withdrawal of the rejections are respectfully requested.

Rejection of Claims 25 and 27 under 35 U.S.C. §112

Claims 25 and 27 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner stated that Claim 25 and by dependency Claim 27 are vague and indefinite in the recitation of "derived from".

As stated above, Claim 25 has been amended by deleting term "derived from".

As stated above, Claim 27 has been amended to depend on Claim 24.

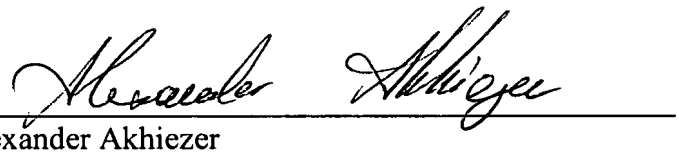
Applicants submit that Claims 25 and 27, as amended are definite. Reconsideration and withdrawal of the rejections are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By 

Alexander Akhiezer
Registration No. 54,617
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133

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